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Evaluation of beractant, poractant alfa and calfactant use in newborns with respiratory distress syndrome: A single-center retrospective study

The use of Surfactants in newborn

Cengizhan Ceylan[1], Seyma Tetik Rama[2, 3], Ayse Huzeyme Cınar[2], Murat Konak[4], Saime Sundus Uygun[4], Mehmet Ozturk[5], Hanifi Soylu[4]
[1] Departmant of Clinical Pharmacy, Faculty of Pharmacy, Selcuk University, Konya
[2] Departmant of Pharmacology, Faculty of Pharmacy, Selcuk University, Konya
[3] Department of Department of Pharmacology, Graduate School of Health Sciences, Ankara University, Ankara
[4] Departmant of Neonatology, Faculty of Medicine, Selcuk University, Konya
[5] Departmant of Radiology, Faculty of Medicine, Selcuk University, Konya, Türkiye

Abstract

Aim: Surfactant production by type II pneumocytes starts at 24-25 weeks of gestation and reaches optimum level at 36-37 weeks. The aim of this study was to retrospectively evaluate the efficacy of three different surfactant preparations on the respiratory functions of preterm infants.

Material and Methods: This study was carried out retrospectively in newborns with respiratory distress syndrome who received inpatient treatment and used surfactant in the Neonatal Intensive Care Unit of Selcuk University Faculty of Medicine, Department of Pediatrics, in 2017-2021. The study group included 111 preterm infants diagnosed with RDS, with a delivery week of 32 and below, who were administered one of three different animal-derived surfactant preparations (poractant alfa, calfactant and beractant).

Results: In this study, poractant alfa was applied to 48.65% (n=54) of the patients, calfactant to 13.51% (n=15), and beractant to 37.84% (n=42) of the patients due to RDS. There was no statistically significant difference between the three different surfactant groups in terms of maternal drug use, antenatal steroid use, which affect the development of RDS in newborns. Gender, type of birth, gestational age, maternal age, 1-min Apgar scores, and 1-, 3-, 5-, and 7-day FiO_2 levels did not differ between the three groups.

Discussion: The efficacy of poractant alfa, beractant and calfactant used in newborns with RDS is similar.

Keywords

Respiratory Distress Syndrome, Surfactant, Poractant Alfa, Calfactant, Beractant

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Corresponding Author: Cengizhan Ceylan, Department of Clinical Pharmacy, Faculty of Pharmacy, Selcuk University, Konya, Türkiye.
E-mail: c.ceylan20@gmail.com P: +90 543 367 02 44
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4164-9212
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Introduction

Pulmonary surfactant is a complex surface-active material found on the alveolar fluid surface of the lungs, which reduces the air-water surface tension in the lungs, facilitating breathing and preventing alveolar collapse [1, 2]. Surfactant production by type II pneumocytes starts at 24-25 weeks of gestation and reaches optimum level at 36-37 weeks [3]. Therefore, immature lungs cannot produce enough surfactant in infants born before 36 weeks of gestation, and diffuse alveolar collapse occurs in the lungs as a result of surfactant deficiency [4]. Respiratory distress syndrome (RDS) is one of the main causes of respiratory failure in premature infants due to insufficient maturation of the lungs and lack of surfactant [5]. Serious complications of RDS include pneumothorax, pulmonary hemorrhage, intraventricular hemorrhage, and bronchopulmonary dysplasia [6]. Tachypnea, subcostal and intercostal retractions, nasal flare, and cyanosis immediately after birth are some of the clinical signs of RDS. Severe cases may require intubation and mechanical ventilation. Diffuse, symmetrical, reticulogranular structures that typically mimic the ground-glass appearance are seen on the chest radiograph . In the management of newborn RDS, a skilled multidisciplinary care team should deliver the best possible respiratory support. For airway and alveolar expansion, adequate oxygenation and ventilation should be provided. Treatment of RDS in preterm newborns with exogenous surfactant replacement therapy significantly reduces the incidence of morbidity, mortality, pulmonary air leak, and pneumothorax. Also, it was found that surfactant treatment in newborns with pneumonia or sepsis showed better gas exchange compared to newborns who did not receive surfactant treatment. Antenatal corticosteroid therapy accelerates fetal lung maturation by increasing the activity of enzymes responsible for surfactant biosynthesis, thus reducing the incidence of neonatal mortality and brain injury. Recommendations of the European Guidelines (2019 update) for Management of Neonatal RDS in Preterm Infants on surfactant administration: premature infants with RDS should be given animal-derived surfactant preparation as soon as possible. CPAP (continuous positive airway pressure) should be initiated early in infants of gestational age less than 30 weeks. If the preterm neonates need mechanical ventilation, it should be targeted for the shortest possible time. If evidence of RDS persists, such as the need for mechanical ventilation, a second, sometimes third dose of surfactant should be administered. Randomized trials show that multiple-dose surfactant treatment strategies lead to a reduction in pneumothorax incidence and mortality compared to single-dose administration.

For now, there are three animal-derived surfactants approved by the Food and Drug Administration for the treatment of newborns diagnosed with RDS in Turkey: poractant alfa (Curosurf ®) in 1998, calfactant (Infasurf ®) in 1998 and beractant (Survanta ®) in 1991. The aim of this study was to retrospectively evaluate the efficacy of three different surfactant preparations on the respiratory functions of preterm infants.

Material and Methods

Study design

This study was carried out retrospectively in newborns with respiratory distress syndrome who received inpatient treatment and used surfactant in the Neonatal Intensive Care Unit of Selcuk University Faculty of Medicine, Department of Pediatrics, in 2017-2021.

The diagnosis of RDS in newborns with clinical manifestations of respiratory distress was evaluated by chest radiography. The diagnosis of RDS was confirmed by ground glass appearance in the lung and blood gas analysis. Surfactant replacement therapy was administered to each patient according to the European Consensus Guidelines [9]. The first doses of poractant alfa 200 mg/kg (recurrent dose of 100 mg/kg if needed), calfactant 100 mg/kg and beractant 100 mg/kg were injected into the trachea via an orogastric tube through an endotracheal tube.

The clinical course of postnatal RDS, newborn delivery type, RDS scoring based on neonatal chest X-ray interpretation, Apgar scores, FiO2 need, oxygen and mechanical ventilation needs, the day of starting oral feeding and the length of stay in the hospital were recorded. Then, the efficacy of three different natural surfactant preparations was evaluated in line with these parameters.

Statistical analysis

Statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) statistical software. One-way analysis of variance (ANOVA) test was applied for continuous variable data for those with normal distribution. The results were considered significant at $p<0.05$ at 95% confidence interval.

Ethical Approval

This study was approved by the local ethics committee of the Selcuk University Faculty of Medicine (Date: 2022-04-12, No: E-70632468-050.01.04-267676).

Results

The study group included 111 preterm infants diagnosed with RDS, with a delivery week of 32 and below, who were administered one of three different animal-derived surfactant preparations (poractant alfa, calfactant and beractant) (Figure 1). Patients who died within the first three days were not included in the study groups.

In this study, poractant alfa was applied to 48.65% (n=54) of the patients, calfactant to 13.51% (n=15), and beractant to 37.84% (n=42) of the patients due to RDS.

In this study, parameters such as gender (male or female), delivery type (normal spontaneous vaginal delivery (NSVD) or cesarean delivery), maternal age, gestational age, birth weight, Apgar scores and FiO2 values were compared according to three different surfactant preparations administered to newborns with RDS (Table 1). Accordingly, 49 of 54 patients in Group-I, 11 of 15 patients in Group-II, and 38 of 42 patients in Group-III were born by cesarean section, and there was no statistical difference between the groups in this respect. The mean birth weight of the neonates was found to be 1135.09 in Group-I, 1509.7 in Group-II and 1368.4 in Group-III. A statistically significant difference was found between the groups in terms of mean birth weight. The mean Apgar scores at the 1-min were found to be 5 in Group-I, 6 in Group-II and 5 in Group-III. No statistically significant difference was found between the groups in Apgar scores at the 1- and 5-min. Gender, type of

birth, gestational age, maternal age and 1-, 3-, 5-, and 7-day FiO2 levels did not differ between the three groups. There was no statistically significant difference in clinical course in terms of tachypnea, cyanosis, moaning while breathing and retraction in newborns treated with surfactant. Details of other evaluated parameters are given in Table 1.

The presence and absence of morbidity parameters such as sepsis, pulmonary hemorrhage, pneumothorax, as well as mortality in newborns with RDS in treatment with different surfactant preparations were evaluated (Table 2). Accordingly, sepsis was positive in 24 of 54 patients in Group-I, 7 of 15 patients in Group-II, and 20 of 42 patients in Group-III. No statistically significant difference was found between the groups between sepsis positive and negative. Pulmonary hemorrhage was was found to be positive in 5 of 54 patients in Group-I, 1 of 15 patients in Group-II, and 1 of 42 patients in Group-III. No statistically significant difference was found between the groups between pulmonary hemorrhage positive and negative. Mortality, which is one of the most important parameters for our study, was evaluated among the groups, was found in 12 of 54 patients in Group-I, 0 of 15 patients in Group-II, and 7 of 42 patients in Group-III. Antenatal steroid use was was found in 20 of 54 patients in Group-I, in 4 of 15 patients in Group-II, and in 20 of 42 patients in Group-III. No statistically significant difference was found between the groups in terms of antenatal steroid use. There was no statistically significant difference in the presence of sepsis, mortality pulmonary hemorrhage, and pneumothorax in the patient groups treated with various surfactants. Regarding maternal drug and prenatal steroid use, both of which have an impact on the development of RDS in neonates, there was no statistically significant difference between the three distinct surfactant groups. Details of other evaluated parameters are given in Table 2.

According to different surfactant preparations applied to newborns with RDS, extubation in the first 3 days, reintubation in 14 days, mechanical ventilation time in the first 28 days, time of dependence on oxygen, time of application of nasal continuous positive airway pressure (NCPAP), day of initiation of oral feeding and hospital stay time were evaluated. When the patients who were extubated in the first 3 days were evaluated, 29 of 54 patients in Group-I, 7 of 15 patients in Group-II and 21 of 42 patients in Group-III were positive. When the total mechanical ventilation time between the groups was compared, it was found that the mean was 18.93 in Group-I, 17.87 in Group-II and 16.26 in Group-III. The mean RDS scores on day 1 were found to be 2.07 in Group-I, 1.69 in Group-II and 1.82 in Group-III.

There was no statistically significant difference in terms of extubation in the first 3 days, reintubation in 14 days, NCPAP administration time, mechanical ventilation time in the first 28 days, oxygen dependent time, day of initiation of oral feeding and hospital stay time between groups of newborns with RDS treated with different surfactants. RDS scoring and the presence of pneumothorax were evaluated by examining the chest radiographs of newborns with RDS treated with different surfactant preparations within the first 3 days. Details of other evaluated parameters are given in Table 3.

Table 1. Comparison of different surfactant preparations evaluated in terms of various parameters.

Evaluated parameters	Group-I Poractant alfa (n=54)	Group-II Calfactant (n=15)	Group-III Beractant (n=42)	p-value
Male, n (%)	28 (51.8)	11 (73.3)	25 (59.5)	0.320
Female, n (%)	26 (48.2)	4 (26.7)	17 (40.5)	0.320
NSVD, n (%)	5 (9.3)	4 (26.7)	4 (9.5)	0.215
Cesarean delivery, n (%)	49 (90.7)	11 (73.3)	38 (90.5)	0.215
Maternal age, mean	28.39	27.6	28.64	0.904
Gestational age (w), mean	28.0	29.0	28.Haz	0.333
Birth weight (w), mean	1135.09	1509.7	1368.4	0.010
1-min Apgar, mean	5	6	5	0.633
5-min Apgar, mean	6	8	7	0.54
1-day FiO_2 value, mean	32	30	29	0.729
3-day FiO_2 value, mean	25.65	22.5	27	0.439
5-day FiO_2 value, mean	26	25	24	0.533
Tachypnea, n (%)	5 (14.7)	2 (18.2)	8 (38.1)	0.126
Cyanosis, n (%)	3 (8.8)	0 (0)	2 (9.5)	0.592
Moaning while breathing, n (%)	23 (67.6)	6 (54.5)	9 (42.8)	0.197
Retraction, n (%)	23 (67.6)	7 (63.6)	11 (52.4)	0.535
Normal course, n (%)	4 (11.8)	3 (27.3)	5 (23.8)	0.379

Table 2. Comparison of morbidity and mortality characteristics according to different surfactant preparations administered to newborns with RDS.

Variables	Group-I Poractant alfa (n=54)	Group-II Calfactant (n=15)	Group-III Beractant (n=42)	p-value
Sepsis, n (%)	Positive 24 (44.4)	Positive 7 (46.7)	Positive 20 (47.6)	0.95
	Negative 30 (55.6)	Negative 8 (53.3)	Negative 22 (52.4)	
Pulmonary hemorrhage, n (%)	Positive 5 (9.2)	Positive 1 (6.7)	Positive 1 (2.4)	0.39
	Negative 49 (90.8)	Negative 14 (93.2)	Negative 41 (97.6)	
Pneumothorax, n (%)	Positive 2 (3.7)	Positive 1 (6.7)	Positive 4 (9.5)	0.51
	Negative 52 (96.3)	Negative 14 (93.2)	Negative 38 (90.5)	
Mortality, n (%)	Positive 12 (22.2)	Positive 0 (0)	Positive 7 (16.7)	-
	Negative 42 (77.8)	Negative 15 (100)	Negative 35 (83.3)	
Maternal hypertension, n (%)	4 (7.4)	0 (0)	5 (11.9)	-
Maternal diabetes, n (%)	3 (5.5)	0 (0)	3 (7.14)	-
Maternal drug use, n (%)	4 (7.4)	2 (13.3)	3 (7.14)	0.629
Antenatal steroid use, n (%)	20 (37.03)	4 4 (26.6)	20 (47.61)	0.676

Table 3. Comparison of changing clinical parameters in newborns with RDS after treatment with different surfactant preparations.

Variables	Group-I Poractant alfa (n=54)	Group-II Calfactant (n=15)	Group-III Beractant (n=42)	p-value
Patient extubated in the first 3 days, n (%)	Positive 29 (53.7)	Positive 7 (46.7)	Positive 21 (50)	0.87
	Negative 25 (46.3)	Negative 8(53.3)	Negative 21 (50)	
Patient re-intubated within 14 days, n (%)	Positive 10 (18.5)	Positive 3 (20)	Positive 6 (14.3)	0.82
	Negative 44 (81.5)	Negative 12 (80)	Negative 36 (85.7)	
NCPAP administration time (days), mean	11.2	8.6	9.5	0.51
Total mechanical ventilation time (days), mean	18.93	17.87	16.26	0.46
Oxygen dependent time (days), mean	18.9	19.93	18.37	0.59
The day of starting oral feeding within 28 days, mean	14.5	13	13	0.85
Hospital stay time (days), mean	56.4	57.2	44.3	0.26
RDS score on day 1, mean	2.7	1.69	1.82	0.43
RDS score on day 2, mean	1.86	1.71	1.65	0.74
RDS score on day 3, mean	1.66	1.67	1.50	0.80
Pneumothorax on day 1, n (%)	Positive 1 (1.9)	Positive 0 (0)	Positive 0 (0)	0.59
	Negative 53 (98.1)	Negative 15 (100)	Negative 42 (100)	
Pneumothorax on day 2, n (%)	Positive 1 (1.9)	Positive 0 (0)	Positive 0 (0)	0.59
	Negative 53 (98.1)	Negative 15 (100)	Negative 42 (100)	
Pneumothorax on day 3, n (%)	Positive 1 (1.9)	Positive 2 (13.3)	Positive 4 (9.5)	0.15
	Negative 53 (98.1)	Negative 13 (86.7)	Negative 38 (90.5)	

Discussion

The severity of RDS, a pulmonary insufficiency syndrome, rises throughout the first two to three days of life and starts immediately after or shortly after birth. Clinically, RDS is characterized by early respiratory distress, including cyanosis, moaning, retraction, and tachypnea. Blood gas analysis can show that respiratory failure is developing, and air bronchograms and the distinctive "ground glass" appearance on chest X-rays can confirm the diagnosis. If left untreated, death occurs due to progressive hypoxia and respiratory failure. RDS is due to structural immaturity of the lung combined with alveolar surfactant deficiency. Although there are studies worldwide to compare the effectiveness of surfactant types used in newborns, studies in our country are limited.

In a study conducted by Yılmaz et al., comparing the efficacy of Poractant alfa, Beractant and Calfactant preparations, sepsis and mortality rates were found to be lower in patients treated with Calfactant. However, in a study by Trembath et al. in which they compared beractant, calfactant, and poractant alfa, there was no difference in outcomes, including air leak, bronchopulmonary dysplasia, and mortality. The researchers thought that surfactants included in previous studies did not show real differences in the efficacy of surfactants in terms of mortality and outcomes and this was related to the variation in outcomes attributed to different institutions. It is considered to be an advantage that the sample size of the calfactant group is larger in the study by Yılmaz et al. In another study conducted in our country, mortality rates of newborns with RDS using poractant alfa and beractant were found to be similar. In our study, no significant difference was found between the sepsis rates of the patients treated with 3 different natural surfactant preparations. No mortality was observed in the group receiving calfactant treatment. This is thought to be related to the high birth weight of the newborns in the calfactant group and their lower numbers compared to the other groups.

In our study, it was observed that the oxygenation of the patients using surfactant improved and their respiratory support requirements decreased, but no significant difference was found between the natural surfactants used. In a randomized controlled study conducted in Iran, pneumothorax and pulmonary hemorrhage were found statistically significant among surfactants [15].

The results of observational studies and clinical studies have shown that antenatal steroids can reduce the need for prophylactic and early surfactant replacement in infants born after 27 to 28 weeks of gestation [16]. In our study, when the relationship between different surfactant preparations and RDS incidence in antenatal steroid use in newborns at and below 32 weeks of gestation was examined, no significant difference was found ($p>0.05$).

In a study comparing the use of poractant alfa and beractant, no statistical significance was found among surfactants in terms of Apgar scores, maternal preeclampsia, mode of delivery, pneumothorax and hemorrhage [17]. The results are in agreement with the data in our study.

In a randomized controlled study conducted by Mishra et al., no relationship was found between the duration of hospital stay and the surfactants used [18]. In our study, there was no significant difference ($p>0.05$) in terms of length of hospital stay and initiation of oral feeding for three different groups.

Another study revealed no difference between surfactants in terms of oxygen consumption, extubation age, problems, hospital stay, and death [19]. The results of our study are compatible with other studies.

In order to provide more reliable data in the comparison of three natural surfactants, randomized controlled studies that keep the sample size as large as possible are needed. In studies comparing 3 natural surfactant preparations, which have already been studied, the samples are quite small. Maximum care should be taken in patient selection. It is thought that more care should be taken when matching the socio-demographic and clinical characteristics of patients treated with different surfactant preparations.

Conclusion

The efficacy of poractant alfa, beractant and calfactant used in newborns with RDS is similar. Studies with homogeneous patient populations between groups are needed to compare efficacy more comprehensively.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest
The authors declare no conflict of interest.

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